Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-11. (Canceled)

12. (Currently amended) A method for identifying a candidate agent that interacts with a beta-amyloid precursor protein (APP) binding site of Beta-site APP Cleaving Enzyme (BACE), the method comprising:

(a) utilizing the relative three-dimensional structural coordinates of a complex of a BACE peptide and an APP inhibitor according to Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of the amino acid residues in the complex not more than 1.5Å, to generate a three-dimensional representation of the complex, wherein:

(i) the BACE peptide in the complex consists essentially of the amino acid sequence of residues 58-447 of SEQ ID NO:1, and

(ii) the APP inhibitor in the complex consists essentially of the amino acid sequence SEVNStaVAEF (SEQ ID NO:3), wherein Sta is (S)-statine;

(b) identifying the amino acid residues forming the APP-binding site of the BACE peptide from the three-dimensional representation in step (a); ~~in order to generate~~

(c) generating a three-dimensional model of the APP-binding site of BACE, wherein the APP-binding site comprises the relative structural coordinates according to Figures lA-1EEE of amino acid residues LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE17l, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291,

THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396, and ILE447, ± a root mean square deviation from the backbone atoms of said amino acid residues of not more than 1.5Å;

~~(c)~~ (d) employing said three-dimensional model from step ~~(b)~~ (c) to identify said candidate agent;

~~(d)~~ (e) obtaining said candidate agent; and

~~(e)~~ (f) contacting *in vitro* or *in vivo* said candidate agent with BACE to determine the ability of said candidate agent to interact or bind to BACE,
whereby the detection of the ability of said candidate agent to interact or bind to BACE identifies said candidate agent.

13. (Previously presented) The method of Claim 12, wherein the ± root mean square deviation from the backbone atoms of said amino acid residues in the complex is not more than 1.0 Å.

14. (Previously presented) The method of Claim 12, wherein the ± root mean square deviation from the backbone atoms of said amino acid residues in the complex is not more than 0.5 Å.

15. (Currently amended) The method of Claim 12, wherein step ~~(c)~~ (d) comprises determining the degree of association between the candidate agent and the three dimensional model of the APP-binding site of BACE.

16. (Previously presented) The method of Claim 12, wherein the contacting of the candidate agent with BACE comprises determining the effect the agent has on BACE activity.

17. (Canceled)

18. (Previously presented) The method of Claim 16, wherein the candidate agent is a potential inhibitor of binding between BACE and APP or an APP peptide.

19. (Previously presented) The method of Claim 18, further comprising contacting the candidate agent with BACE in the presence of APP or the APP peptide.

20. (Currently amended) A method for identifying a candidate agent that interacts with a beta-amyloid precursor protein (APP) binding site of Beta-site APP Cleaving Enzyme (BACE), the method comprising:

(a) utilizing the relative three-dimensional structural coordinates of a complex of a BACE peptide and an APP inhibitor according to Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of the amino acid residues in the complex of not more than 1.5Å, to generate a three-dimensional representation of the complex,

wherein the BACE peptide in the complex consists essentially of the amino acid sequence of residues 58-447 of SEQ ID NO:1, and the APP inhibitor in the complex consists essentially of the amino acid sequence SEVNStaVAEF (SEQ ID NO:3), wherein Sta is (S)-statine;

(b) identifying the amino acid residues forming the APP-binding site of the BACE peptide from the three-dimensional representation in step (a); ~~in order to generate~~

(c) generating a three-dimensional model of the APP-binding site of BACE, wherein the APP-binding site comprises the relative structural coordinates according to Figures lA-1EEE of amino acid residues LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE17l, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396, and ILE447, ± a root mean square deviation from the backbone atoms of said amino acid residues of not more than 1.5Å;

~~(c)~~ (d) employing said three-dimensional model from step ~~(b)~~ (c) to identify said candidate agent;

~~(d)~~ (e) synthesizing said candidate agent; and

~~(e)~~ (f) contacting said candidate agent with ~~the three-dimensional model of the APP-binding site of the~~ BACE to determine the ability of said candidate agent to interact or bind to BACE,
whereby the detection of the ability of said candidate agent to interact or bind to the BACE peptide identifies said candidate agent.

21. (Previously presented) The method of Claim 20, wherein the ± root mean square deviation from the backbone atoms of said amino acid residues in the complex is not more than 1.0 Å.

22. (Previously presented) The method of Claim 20, wherein the ± root mean square deviation from the backbone atoms of said amino acid residues in the complex is not more than 0.5 Å.

23. (Currently amended) The method of Claim 20, wherein step ~~(c)~~ (d) comprises determining the degree of association between the candidate agent and the three dimensional model of the APP-binding site of BACE.

24. (Previously presented) The method of Claim 20, further comprising contacting the candidate agent with BACE in order to determine the effect the agent has on BACE activity.

25. (Canceled)

26. (Previously presented) The method of Claim 24, wherein the candidate agent is a potential inhibitor of binding between BACE and APP or an APP peptide.

27. (Previously presented) The method of Claim 26, further comprising contacting the candidate agent with BACE in the presence of APP or an APP peptide.

28-32. (Canceled)

33. (Canceled)

34. (Previously presented) The method of Claim 12, wherein obtaining the agent comprises synthesizing the agent.

35. (Canceled)

36. – 40. (Canceled)

41. (Currently amended) ~~The method of Claim 12,~~ A method for identifying a candidate agent that interacts with a beta-amyloid precursor protein (APP) binding site of Beta-site APP Cleaving Enzyme (BACE), the method comprising:

(a) utilizing the relative three-dimensional structural coordinates of a complex of a BACE peptide and an APP inhibitor according to Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of the amino acid residues in the complex not more than 1.5Å, to generate a three-dimensional representation of the complex, wherein:

(i) the BACE peptide in the complex consists essentially of the amino acid sequence of residues 58-447 of SEQ ID NO: 1;

(ii) the APP inhibitor in the complex consists essentially of the amino acid sequence SEVNStaVAEF (SEQ ID NO:3), wherein Sta is (S)-statine; and

~~wherein~~ (iii) the three-dimensional structural coordinates of the complex of the BACE peptide and the APP inhibitor according to Figures 1A-1EEE were obtained by subjecting a co-crystal comprising the BACE peptide in complex with the APP inhibitor to X-ray diffraction and collecting data sufficient to determine the three-dimensional coordinates of said complex, wherein said co-crystal has space group I222, and unit cell parameters a=86.627, b=130.861, c=130.729, and $\alpha=\beta=\gamma=90°$;

(b) identifying the amino acid residues forming the APP-binding site of the BACE peptide from the three-dimensional representation in step (a);

(c) generating a three-dimensional model of the APP-binding site of BACE, wherein the APP-binding site comprises the relative structural coordinates according to Figures lA-1EEE of amino acid residues LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE17l, ASN172,

SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396, and ILE447, ± a root mean square deviation from the backbone atoms of said amino acid residues of not more than 1.5Å;

(d) employing said three-dimensional model from step (c) to identify said candidate agent;

(e) obtaining said candidate agent; and

(f) contacting *in vitro* or *in vivo* said candidate agent with BACE to determine the ability of said candidate agent to interact or bind to BACE,

whereby the detection of the ability of said candidate agent to interact or bind to BACE identifies said candidate agent.

42. (Canceled)

43. (Canceled)

44. (New) A method for identifying a candidate agent that interacts with a beta-amyloid precursor protein (APP) binding site of Beta-site APP Cleaving Enzyme (BACE), comprising:

(a) utilizing the relative three-dimensional structural coordinates of a complex of a BACE peptide and an APP inhibitor according to Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of the amino acid residues in the complex of not more than 1.5Å, to generate a three-dimensional representation of the complex, wherein the BACE peptide in the complex consists essentially of the amino acid sequence of residues 58-447 of SEQ ID NO:1, and the APP inhibitor in the complex consists essentially of the amino acid sequence SEVNStaVAEF (SEQ ID NO:3), wherein Sta is (S)-statine;

(b) identifying the amino acid residues forming the APP-binding site of the BACE peptide from the three-dimensional representation in step (a);

(c) generating a three-dimensional model of the APP-binding site of BACE, wherein the APP-binding site comprises the relative structural coordinates according to Figures lA-1EEE of amino acid residues LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE17l, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396, and ILE447, ± a root mean square deviation from the backbone atoms of said amino acid residues of not more than 1.5Å;

(d) employing said three-dimensional model from step (c) to identify said candidate agent;

(e) obtaining said candidate agent; and

(f) contacting said candidate agent with the three-dimensional model of the APP-binding site of the BACE to determine the ability of said candidate agent to interact or bind to BACE, whereby the detection of the ability of said candidate agent to interact or bind to the BACE peptide identifies said candidate agent.